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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,712	10/27/2003	Hideki Taniguchi	25682	2281

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NATH & ASSOCIATES
112 South West Street
Alexandria, VA 22314

EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,712	TANIGUCHI ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-24, 30-37, 40-55, and 57-90* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13,18-21,30,31,40-48,51,52,75,76,79,80,83-85 and 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 12,14-17,22-24,32-37,49,50,53-55, 57-74,77,78,81,82,86,87,89 and 90.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/07/2007 has been entered.

2. Claims 1-10, 25-29, 38, 39, and 56 have been cancelled.

Claims 12, 14-17, 22-24, 32-37, 49, 50, 53-55, 57-74, 77, 78, 81, 82, 86, 87, 89, and 90 have been withdrawn. It is noted that claim 12 directly or indirectly depends from the withdrawn claims 78 and 90; therefore, although claim 12 is identified as "previously presented", the claim is withdrawn from further consideration.

Claims 11, 13, 18-21, 30, 31, 40-48, 51, 52, 75, 76, 79, 80, 83, 84, 85, and 88 are under examination.

3. The objection to claims 11, 13, 30, 31, and 40-48 as being directly or indirectly dependent from subsequent claims is withdrawn in response to Applicant's arguments filed on 12/07/2007.

Priority

4. Acknowledgment is made of Applicant's submission of an English language translation of the priority document, PCT/JP0204084. Applicant also provided a statement that the translation of the certified copy is accurate in accordance with 37 C.F.R. 1.55. Therefore, the priority date for the instant application is 03/24/2001.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 11, 13, 18-21, 30, 31, 40-48, 51, 52, 75, 76, 79, 80, 83, 84, 85, and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramiya et al. (Nature Medicine, 2000, 6: 278282, of record), in view of each Serup (Nature Genetics, 2000, 25: 134-135, of record), Oberg-Welsh et al. (Pancreas, 1996, 12: 334-339, of record), and Suzuki et al. (Hepatology, 2000, 32: 1230-1239, of record).

Ramiya et al. teach a method of obtaining pancreatic ductal stem cells expressing c-Met by culturing single cell suspensions isolated from the digested pancreatic tissue (claims 75 and 76) (Abstract, p. 279, column 1). Ramiya et al. teach that the pancreatic ductal stem cells are able to produce functioning islets and therefore they could provide an abundant islet source for the treatment of type I diabetes (Abstract, p. 278, column 2). Ramiya et al. do not teach separating or identifying the pancreatic stem cells by using antibodies against c-Met c-kit, CD45, and TER119

(claims 76) or antibodies against c-Met c-kit, CD45, TER119, and Flk-1 (claim 75). However, this is not innovative over the prior art because the prior art teaches or suggests using the markers above to isolate pancreatic stem cells, as follows: **(i)** Ramiya et al. teach that pancreatic stem cells express c-Met, **(ii)** Oberg-Welsh et al. teach that c-kit and Flk-1 are expressed in the fetal pancreatic ducts (Abstract, p. 336, column 2, p. 337, column 2, second paragraph); since the prior art teaches that the pancreatic stem cells reside in the ducts (see Ramiya et al., Abstract, p. 278, column 1; Serup, p. 134, column 1, second paragraph), the combination of Oberg-Welsh et al. and Serup suggests that c-kit and Flk-1 are pancreatic stem cells markers, and **(iii)** Suzuki et al. teach that hematopoietic stem cells express CD45 and TER119 and teach the using antibodies directed against CD45 and TER119 to exclude contaminating hematopoietic cells expressing these markers from stem cell preparations, i.e., to select for $CD45^-$ $TER119^-$ cells (p. 1231, column 1, second paragraph, p. 1232, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to use antibodies directed against c-Met, c-kit, CD45, and TER119 or against c-Met, c-kit, CD45, TER119, and Flk-1 to separate the pancreatic stem cells from the single cell suspension of Ramiya et al., with a reasonable expectation of success (claim 75). The motivation to isolate pancreatic stem cells is provided by Serup, who teaches the need of identifying identifying reliable surface markers for obtaining *bona fide* pancreatic stem cells for therapy (Abstract, p. 134, column 1 bridging column 2, and column 3, p. 135, column 3). One of skill in the art would have been motivated to use a combination of markers because the art teaches that more than one marker is needed to separate stem

cells. One of skill in the art would have been expected to have a reasonable expectation of success in isolating these cells because the art teaches the successful use cell surface markers to isolate stem cells.

Claims 18, 20, 21, 30, 40, 42-45, and 88 disclose a specific phenotype for the pancreatic stem cells, i.e., c-Met$^+$ c-kit$^-$ CD45$^-$ TER119$^-$ (i.e., cells isolated by the method of claim 75). According to the teachings above, one of skill in the art would have had expected that cells having the phenotype c-Met$^+$ CD45$^-$ TER119$^-$ would be pancreatic stem cells. The limitation of fractionating the cells according to expression of c-Met and c-kit (claims 79 and 80) is not innovative over the prior art since this is the standard procedure in isolating stem cells by flow cytometry. For example, Suzuki et al. teach separating hepatic stem cells by fractionating the population by c-kit expression, assessing each population for ability to form colonies (i.e., stem cell potential) and finding that, although they expected the cells expressing c-kit to have stem cell potential, the c-kit$^-$ cells were the ones with the ability to form colonies, i.e., having stem cell potential (p. 1230, column 2 bridging p. 1231, columns 1 and 2). According to these teachings, one of skill in the art would have had known to further fractionate the cells into c-kit$^+$ cells and c-kit$^-$ cells and assess their clonogenic potential to identify the pancreatic progenitor cell. With respect to c-Met, one of skill in the art would have been motivated to separate the cells into c-Met$^-$ and c-Met$^+$ and select for c-Met$^+$ cells because the art Ramya et al. teach that pancreatic stem cells express c-Met. Therefore, one of skill in the art would have had easily identified c-Met$^+$ c-kit$^-$ CD45$^-$ TER119$^-$ cells as the pancreatic stem cells. With respect to the limitation of a cloned

pluripotent pancreatic stem cell (claims 18, 20, and 21), since the stem cell potential is assesses by the ability to form colonies, the isolated pancreatic stem cells taught by the prior art cited above are cloned pluripotent stem cells. With respect to the limitation of a pharmaceutical composition (claim 20), the buffer used to isolate the viable pancreatic stem cells is considered a pharmaceutical composition.

Claims 11, 13, 19, 31, 41, 46-48, 51, and 52 disclose the specific phenotype of c-Met$^+$ c-kit$^-$ CD45$^-$ TER119$^-$ Flk-1$^-$ (i.e., cells isolated by the method of claim 76). Again, further fractionating the c-Met$^+$ c-kit$^-$ CD45$^-$ TER119$^-$ cells into Flk$^-$ and Flk$^+$ and assessing their stem cell potential is not innovative over the prior art since this is a standard procedure in isolating stem cells by flow cytometry (see above). One of skill in the art would have had known to further fractionate the c-Met$^+$ c-kit$^-$ CD45$^-$ TER119$^-$ into Flk-1 positive and negative cells and assess their clonogenic potential to identify the pancreatic progenitor cell because Flk-1 is suggested by the prior art as a pancreatic stem cell marker. By doing such, one of skill in the art would have necessarily practiced the method of claims 83-85. Therefore, one of skill in the art would have had easily identified c-Met$^+$ c-kit$^-$ CD45$^-$ TER119$^-$ Flk-1$^-$ cells as the pancreatic stem cells. With respect to the limitation of a cloned pluripotent pancreatic stem cell (claims 19, 51, and 52), since the stem cell potential is assesses by the ability to form colonies, the isolated pancreatic stem cells are cloned pluripotent stem cells. With respect to the limitation of a pharmaceutical composition (claim 51), the buffer used to isolate the viable pancreatic stem cells is considered a pharmaceutical composition.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant asserts that the Examiner did not establish a *prima facie* case of obviousness because (i) there is no motivation supporting the combination of Suzuki et al. with Ramiya et al., Serup, and Oberg-Welsh et al. because Suzuki et al. is concerned with hepatic cells, whereas the remaining references are concerned with pancreatic cells, and (ii) the cited references do not teach or suggest all the claim limitations because none of them teaches or suggests contacting the pancreatic cells with antibodies against c-Met, c-Kit, CD-45, TER119, and Flk-1. With respect to Ramiya et al., Applicant argues that they teach the *in vitro* growth of islets from stem cells and the detection of transcripts for at least 20 factors by RT-PCR (p. 279), without providing any motivation or suggestion to select c-Met from the 20 described factors. With respect to Serup, Applicant argues that the reference teaches that pancreatic stem cells express the neural stem cell marker nestin and also that there is a lack of established pancreatic stem cell markers; by teaching that none of the markers is reliable surface markers for pancreatic stem cells, Serup teaches away from the selection of any specific marker. At most, applicant argues, Ramiya et al. and Serup et al. suggest trying all 21 factors in an attempt to establish markers for pancreatic stem cells. With respect to Oberg-Welsh et al., Applicant argues that they describe Flk-1, FGFR-4, the IGF-1 receptor, c-kit, and the cytoplasmic tyrosine kinase Jak2 and Trk-A. Applicant submits that Oberg-Welsh et al. do no provide any motivation to select c-kit

from the six factors above, let alone to combine it with one factor (i.e., c-Met) out of the 20 described by Ramiya et al. At most, Applicant argues, the three references suggest using all 27 factors. With respect to Suzuki et al., Applicant argues that they do not teach or suggest any marker for pancreatic stem cells. Therefore, Applicant argues, none of the references, alone or in combination suggests selecting the claimed markers.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

The instant claims are drawn to the isolation of viable pancreatic stem cells which requires using antibodies against specific markers exposed on the cell surface. While pancreatic stem cells also express specific intracellular markers, the use of antibodies directed against such markers requires membrane permeabilization which results in cell death; therefore, one of skill in the art would know that antibodies directed against intracellular markers cannot be used to isolate viable cells. With respect to Ramiya et al., although they teach that the pancreatic stem cells express 20 transcripts, most of their transcripts encode either intracellular or secreted proteins (p. 279). One of skill in the art would not have been motivated to use intracellular markers for the reasons stated above; one of skill in the art would know that secreted proteins cannot be used to isolate any cell since they are released into the extracellular space and are not associated with the cell. From the cell surface proteins taught by Ramyia et al., insulin, insulin receptor, and glucose transporter 2 are also expressed by the endocrine and exocrine pancreas (devoid of pancreatic stem cell) and therefore, one skill in the art would know that these cell surface proteins are not specific markers for pancreatic stem

cells and would not have been motivated to use them to separate pancreatic stem cells. What remains is c-Met, a cell surface marker known taught by the prior art to be expressed by stem cells; the prior art also teaches the use of c-Met to isolate stem cells. Therefore, by reading Ramyia et al., one of skill in the art would have known and be motivated to use c-Met to isolate pancreatic stem cells. With respect to Oberg-Welsh et al., Applicant argues that they describe Flk-1, FGFR-4, the IGF-1 receptor, c-kit, and the cytoplasmic tyrosine kinase Jak2 and Trk-A and provide no motivation to select c-kit from the six factors above. As Applicant points out, Jak2 and Trk-A are intracellular, and therefore, one of skill in the art would not use them to isolate viable pancreatic stem cells. Oberg-Welsh et al. teach that FGFR-4 is ubiquitously expressed in the endocrine and exocrine pancreas and also in pancreatic ducts (Abstract, p. 336, column 2, third full paragraph); therefore, one of skill in the art would not consider FGFR-4 as a specific marker and would not use it to isolate pancreatic stem cells. Since IGF-1 receptor is taught by the prior art to be also expressed by the endocrine pancreas (see Fenmann et al., Metabolism, 1966, 45: 759-766, Abstract), one of skill in the art would understand that IGF-1 receptor could not be used as a specific marker for pancreatic stem cells. On the other hand, Oberg-Welsh et al. teach that Flk-1 and c-Kit are specifically expressed in the pancreatic ducts where pancreatic stem cells reside (Abstract, p. 337, column 2, last paragraph). Therefore, from the proteins taught by Oberg-Welsh et al., one of skill in the art would be motivated to only select Flk-1 and c-Kit. With respect to Serup, it is noted that, although nestin is considered a specific marker for pancreatic stem cells, nestin is an intracellular protein (see Prasad et al., Int J Oncol, 1999, 14:

563-770, Abstract); therefore, one of skill in the art would know that nestin could not be used to isolate viable pancreatic stem cells. The fact that Serup teaches the absence of reliable cell surface markers does not mean that they teach away from the selection of any specific marker, as Applicant argues. On the contrary, Serup teaches the need to identify and use cell surface markers for the isolation of pancreatic stem cells. By reading Serup, one of skill in the art would have been motivated to look for a reliable combination of cell surface markers to be used for the isolation of pancreatic stem cells; the combination of markers is suggested by the prior art, as set forth above, i.e., c-Met, c-kit, and Flk-1. Finally, the fact that Suzuki et al. teach isolating hepatic progenitor cells and do not teach or suggest any marker for pancreatic stem cells is irrelevant. Suzuki et al. teach that CD45 and TER119 are expressed by the hematopoietic cells and they use these cell surface markers to eliminate $CD45^+$ $TER119^+$ cells from their hepatic stem cell population (p. 1231, column 1, third full paragraph, p. 1232, column 1, second paragraph). Based on the teachings of Suzuki et al., one of skill in the art would have known to use CD45 and TER119 to eliminate contaminating $CD45^+$ $TER119^+$ hematopoietic cells from any stem cells preparation, including pancreatic stem cell preparations.

In conclusion, the prior art above suggests using antibodies against c-Met, c-kit, Flk-1, CD45, and TER119 to isolate pancreatic stem cells.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Fenmann et al. (Metabolism, 1966, 45: 759-766, Abstract) and Prasad et al. (Int J Oncol, 1999, 14: 563-770, Abstract) were cited in response to Applicant's argument that one of skill in the art would not have been motivated to specifically select the claimed markers from those taught by the prior art. More specifically, the references were provided to demonstrate that at the time of filing functional and structural aspects of IGF-1 receptor and nestin were known and would be appreciated by the skilled artisan in the context of the claimed invention.

8. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Joseph Woitach/

Joseph Woitach

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